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Psychobiological response to an anger induction task in schizophrenia: The key role of anxiety

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ABSTRACT

In this study an anger induction laboratory task was applied to men with schizophrenia, and resulted in significant changes in different psychophysiological parameters that were measured in a pre-post design. We observed a significantly greater self-reported anger mood and negative affection, lower self-reported positive affection, an increase in cardiovascular reactivity (with blood pressure in deeper affection compared to controls), higher salivary testosterone levels, lower salivary cortisol levels, and an increase in right ear items reported in dichotic listening. Furthermore, clinical risk factors related to anger in our patients were analyzed by Stepwise Regression analyses. Trait anger was significantly associated with a higher level of delusional pathology and impulsivity. Regarding the resulted state of anger as an output of the induction, the most relevant finding was that anxiety consistently and significantly predicted the increasing in anger feelings, and, remarkably, it predicted also the increasing in T levels and the cardiovascular reactivity of the patients.

1. Introduction

A meta-analysis of 204 studies by Douglas et al. (2009) reported that psychosis increases the odds of violence threefold to fourfold, and there is consensus in the literature about a modest but consistent association between aggression and schizophrenia (SZ) (Fazel et al., 2009; Large and Nielssen, 2011). SZ patients carry stigmatization due to the belief that anger in them is a matter of dangerous unpredictability (Ringer and Lysaker, 2014). Focusing our interest in clinical risk factors for violence (apart from social, demographical or biographic), a meta-regression of 110 studies involving 45,533 psychotic patients showed impulsivity as well as psychotic symptomatology (delusions, hallucinations, hostility, and lack of insight) as key factors (Witt et al., 2013). Regarding mood disorders, animal studies connect excessive aggression with disturbed emotional regulation, such as abnormal levels of anxiety (Neumann et al., 2010). In fact, higher anxiety has been associated with higher anger expression (both inwardly and outwardly) in patients with SZ (Ringer and Lysaker, 2014) and one study found a correlation of panic attacks and hostility in chronic SZ (Chen et al., 2001). Additionally, an interesting study found that serious violence (3.6%) was associated with psychotic together with depressive symptoms (Swanson et al., 2006). Despite anger and aggression in SZ being important, little observations are done in a controlled situation of having a patient experiencing anger. This can be easily achieved by using mood induction procedures. In our laboratory, we conducted an experiment applying the Anger Induction (AI) method of Engebretson et al. (1999) to a sample of healthy men, to observe they indeed informed to be feeling angry and in a negative mood after the AI (Herrero et al., 2010). The study was remarkable because a bunch of physiological: Heart Rate (HR) and Blood Pressure (BP), hormonal: Testosterone (T) and Cortisol (C), and cognitive: Dichotic Listening (DL) variables were measured, pre and post AI.

Among these variables, differential cardiovascular reactivity during fear and anger has been reported: In fear response, peripheral vascular

Abbreviations: SZ, schizophrenia; AI, anger induction; HR, heart rate; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; T, testosterone; C, cortisol; T/C, testosterone to cortisol (T/C) ratio; DL, dichotic listening; RH-LH, right hemisphere – left hemisphere; RE -LE, right ear – left ear; REA, right ear advantage; LI, laterality index; HPA, Hypothalamus-Pituitary-Adrenal; HPG, Hypothalamus-Pituitary-Gonadal; PANSS, Positive and Negative Syndrome Scale; PANAS, Positive and Negative Affect Schedule; PA-NA, positive –negative affect; STAXI-2, State-Trait Anger Expression Inventory-2

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resistance decreases keeping diastolic blood pressure (DBP) relatively low. Anger produces increases on HR and SBP as well as peripheral vascular resistance, thus differentially elevating DBP (Schwartz et al., 1981). In our study (Herrero et al., 2010) there was a significant increase in HR as well as in DBP, and a higher nonsignificant mean in SBP after the AI. Regarding endocrine variables, moderately evidence for a role of T in human aggression do exist: greater T levels are associated with anger and interpersonal dominance and hormonal treatments that increase T levels are capable to increase anger, hostility and aggression (Archer, 2006; Carré et al., 2017; O' Connor et al., 2004; Wirth and Schultheiss, 2007). On the other hand, C is positively related to some negative emotions: e.g. fear, sadness and stress (van Honk et al., 2003; Gadea et al., 2005; Borráz-León et al., 2017; Williams et al., 2017) but its relation with anger is weaker than anger with T. Kalin (1999), using primate models to understand human aggression, pointed that offensive aggression is approach motivated and associated with high levels of T and low levels of C. Subsequently, that pattern was found in humans, known as "dual-hormone hypothesis" (Metha and Prasad, 2015). In humans it is known that, during adulthood, activation of the Hypothalamus-Pituitary-Adrenal (HPA) axis suppresses the activity of the Hypothalamus-Pituitary-Gonadal (HPG) axis, and hence high cortisol is related to lower testosterone (Terburg et al., 2009). The above mentioned hypothesis therefore points a high testosterone to cortisol (T/C) ratio would lead to increased attention to threatening cues, low sensitivity to stress, decreased emotional recognition, and a salience of dominance and approach motivation. In addition, other factors such as age, dominance, trauma history, oxytocin levels, or gender (the above scenario would apply mainly to men) mediate the association between T and C levels and anger (Carré and Archer, 2018; Rosell and Siever, 2015; Fragkaki et al., 2018). In our sample of healthy men (Herrero et al., 2010) we found both significant T increases and C decreases after the AI, thus supporting the dual-hypothesis model. Lastly, we were interested in the lateralized-behavioral outcome of the AI. Induced sadness has proved to benefit the performance of right hemisphere (RH) tasks (Bartolic et al., 1999) and left ear items perception in DL (Gadea et al., 2005) possibly due to an activation of RH by the negative emotion triggered an attentional bias to the left hemi-space (see the model of Hugdahl (2003) for theories on attentional asymmetries). However, about anger there is a controversy (Gadea et al., 2011) because despite we could consider anger as an approach emotion, thus preferentially processed by the left hemisphere (LH) (Harmon-Jones, 2007), anger could produce withdrawal behavior, depending on an individual's preferred mode of anger expression (Waldstein et al., 2000). Our healthy men receiving the AI task showed a higher Right Ear Advantage (REA) after the induction, due exclusively to an increase in Right Ear (RE) items, indicating that, in them, anger was linked to LH activation (Herrero et al., 2010).

To date, no published study has examined the consequences of premeditatedly inducing an anger mood in a sample of patients with SZ, measuring the emotional, hormonal, cardiovascular, and brain-lateralization consequences after the induction. Our main aim, therefore, was to explore whether the patients would react similarly to healthy normal controls to such equal procedure. If this is so, we expected increases in anger and negative mood and decreases of positive mood after the induction, together with an increased cardiovascular reactivity, and both a higher T and lower levels of C. We also predict that the anger induction would increase the left hemisphere activity, so a facilitation of RE performance on the DL task would occur. Another aim of the present study was to explore whether any risk factor exists, among clinical symptomatology of the patients, related to their reaction. Based on the literature, we hypothesize those factors regarding positive symptoms and mood psychopathology would be predictors of a higher sensitivity to the induction, and so of a greater psychophysiological reaction.

2. Method

2.1. Subjects

A total of 34 male patients with SZ (DSM-V) and between 18 and 47 years old (mean age: 33.44, SD: 7.09) were recruited from the Valencia Clinic University Hospital (Spain). Diagnoses were made by consensus of two senior clinical psychiatrists. The duration of their illness was in a range of 1 to 30 years (mean 11.5 years, SD 7.3), and the age of their illness onset was among 16 – 32 years. The patients had no history of cardiac illness, traumatic brain injury, epilepsy, neurological or psychiatric history other than schizophrenia. All of them were under treatment with stable doses of antipsychotic medication: 30 with second-generation antipsychotic, and 4 with combined treatment (first and second-generation antipsychotic). None of them had problems with the law or arrest due to violent behavior in the past. None of them had a history of suicidal behavior. The patients were clinically assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) in the last 24 hours before the experiment, by their habitual clinician (not the same who performed the experiment). The Mean (SD) and [range] scores for clinical data were as follows: PANSS Total Scale: 69.50 (13.12) [44–95]. PANSS Negative symptoms: 14.21 (4.13) [7–2]. PANSS Positive symptoms: 18.91 (6.13) [8–31]. PANSS psychopathology: 36.38 (6.26) [21–49]. Three patients (8.8%) scored moderate-severe in the hostility subscale of the PANSS. All patients were right-handed as measured with the Edinburgh Questionnaire (Olfield, 1971). None of them had any imbalance in hearing levels of more than 10 dB (range of frequencies 500/6000 Hz) as determined by a Lafayette 15,014 C screening audiometer. All patients had, at least, completed secondary school studies, and some of them were University students ($N = 6$). All patients gave written informed consent and all procedures were in accordance with the standards of our institutional committee of ethics in research with humans and with the 1964 Helsinki declaration and its later amendments.

The results of the experiment were compared with those obtained previously, where we had applied an identical procedure to a sample of healthy participants, in our laboratory (see details in Herrero et al., 2010). In that study, thirty right-handed men, undergraduate volunteers between 18 and 30 years old (mean age: 22.93, SD: 2.68) performed the same task applied here to the SZ patients). There were no significant differences between such healthy controls and the present sample of patients in gender (all males), laterality (all right handed), and ethnical group (all Caucasian). The difference in mean age of the samples ($T = -7.6$; $p < 0.001$) was controlled through statistical methods (ANCOVA) when necessary.

2.2. Materials

2.2.1. Anger induction procedure

A Spanish adaptation of the Anger Induction (AI) tool of Engebretson et al. (1999) was used to generate an anger experience. Such task exhibited good sensitivity and specificity in that it induced moderate to greater increases in anger (>1 SD change) in 68% of the sample (Engebretson et al., 1999). The procedure consists of 50 self-referent statements gradually progressing from relative mood neutrality ("Today is no different from any other day") to extremely angry ("I am consumed with hatred") connoting irritability, hostility, rage and anger. The patients were given a loose-leaf binder each page of which contained one of 50 anger statements. The instructions were to read each sentence silently, imagine what the sentence is saying, recall any relevant memories, and generally try as much as possible to get into the mood suggested by the sentence. After 20 sec the experimenter continued with the next sentence

2.2.2. Mood scales

2.2.2.1. PANAS scales. We applied a Spanish translation (Sandín et al.,

1999) of the short PANAS (Positive and Negative Affect Schedule) scales (Watson et al., 1988) to assess self-reported mood. The short PANAS consists of two 10-item scales, rated on a 5-point Likert, that comprise positive (PA) and negative (NA) affect states. High PA reflects energy, full concentration and pleasurable engagement, whereas high NA reflects feelings of upset, guilt, fear, anger and nervousness.

2.2.2.2. State-Trait Anger Expression Inventory-2, STAXI-2. We applied a Spanish adaptation (Miguel-Tobal et al., 2001) of the State-Trait Anger Expression Inventory-2, STAXI-2 (Spielberger, 1999) to asses self-reported anger levels. The STAXI-2 measures State of Anger (15 items rated on a 4-point Likert, defined as a transient emotional condition of subjective feelings that can vary from a moderate annoyance to an intense rage) and Trait of Anger (10 items rated on a 4-point Likert, regarding individual differences in perceiving situations as annoying or frustrating and by the tendency to respond to such situations with increased anger).

2.2.3. Cardiovascular response

We analyzed Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Heart Rate (HR), with a Dinamap Procare 100 Vital Signs Monitor (Critikon, Tampa, FL,) which uses the oscilometric principle for pressure determinations; it has digital displays (thus reducing observer error) and an electrical pump. For all the measures, the BP cuff was placed on the nondominant arm (left). The measures were calculated as an average of 3 readings in a row.

2.2.4. Hormonal determinations: salivary testosterone (T) and cortisol (C)

Saliva was collected directly from the mouth using sterile glass tubes for samples of T and Salivette for C (Sarstedt, Rommelsdorf, Germany). The samples were centrifuged (5000 rpm, 15 ± 2 °C) and frozen at –20 °C at the end of each experimental session, until they were analyzed by an experienced technician who was unaware of the hypotheses tested. All samples were analyzed in duplicate and the samples of each subject were included in the same test. The chemiluminescence immunoassay (LIA) with the reagent kit saliva ELISA (Diagnostics Biochem Canada Inc.) was applied in the case of T determinations. The sensitivity of the T assay was 1 pg / mL and the values were expressed in pmol / L. In addition, good precision was obtained, with coefficients of intra- and inter-assay variation of 3.98% and 7.98%, respectively. For C determinations, a radioimmunoassay (RIA) using the Coat-A-Count cortisol reagent kit (DPC-Siemens Medical Solutions Diagnostics) was applied. The sensitivity of the C assay was 0.5 ng / dL and the values were expressed in nmol / L. The coefficients of intra and inter-test variation were 4.3% and 5.2%, respectively.

2.2.5. Perceptual asymmetry: dichotic listening (DL) test

The dichotic stimuli consisted of the six stop consonants paired with the vowel /a/ to form six consonant vowel syllables (ba, da, ga, ka, pa, ta) which were paired with each other to form 30 different syllable pairs, duplicated and recorded randomly; giving 60 test trials with a maximum correct score of 60. The DL test used in this study has achieved a test-retest reliability of 0.86 (for details see Gadea et al., 2005). The test was replayed to the patients from a Sony Walkman D-EJ985 portable CD player with Technics rp-DJ1210 stereo covered outer ear headphones, at a level of 75 dB. The patients were informed that different syllables would be presented to each ear simultaneously and were asked to report only the syllable perceived most clearly. The data were acquired as correctly reported items from the right (RE) and left (LE) ear.

2.3. Procedure

The experiment was programmed for the day after the main control clinical visit of the patient to the hospital once confirmed the patients have slept normally and they were not in any special mood (negative or positive). Patients were advised not to eat, drink, smoke (if possible) or brush their teeth for 1 h prior to testing, and were informed that they would be providing saliva for hormonal analyses, and doing some behavioral tasks in a sound-attenuated room of the hospital. After obtaining written informed consent, the patients filled in the general-information and the handedness questionnaires, and were tested for hearing acuity. Then, we started collecting the pre-AI measures (dependent variables): 3 measures of BP and HR (6 min), PANAS and STAXI-2 State and Trait Scales (5 min), collection of saliva sample (5 min), and performance of the DL test (15 min). Then, a short break of 10 min maximum was given if necessary. After the break the AI task was carried out for 20 min (independent variable). Immediately after the task all dependent variables (post-AI measures) were collected again (except the STAXI-2 Trait subscale). All sessions were carried out in the afternoon, between 1600 to 1800 h in order to control hormonal circadian rhythms and over a 2-month period.

2.4. Statistical analyses

The difference between pre and post AI was tested with a Student's *t* test for related variables, applied to raw scores: PA scale, NA scale, STAXI-2 State scale, HR, SBP, DBP, T, C, LI, with size effects estimations by Cohen's d. In addition, a 2 (right or left ear) * 2 (pre or post) repeated measures ANOVA was applied to DL raw scores (from RE and LE, before and after the AI). We performed subtractions between the post and pre IA values for all the variables (labeled as “subNa”, “subPA”, and so on). Then we used this transformed variables in order to compare the magnitude of the change, after the AI, of the patients with the controls, by applying a Student t test, correlations, and ANCOVA when necessary (data for controls taken from Herrero et al., 2010). Finally, to evaluate the influence of clinical symptoms (PANSS scores) on the patient's response to the AI, we applied a series of Stepwise Regression Analyses (with probability to enter $F = 0.050$ and to remove $F = 0.100$). All statistical analyses were performed on a PC, using the SPSS 24 statistical package set. Data are presented as means and standard deviations (SD).

3. Results

3.1. Consequences of the AI task in patients with SZ (see Table 1)

3.1.1. Mood scales scores

PA scores diminished significantly (t (33) = 3.60, $p < 0.001$; $d = 0.62$), while NA scores increased significantly (t (33) = −5.39, $p < 0.001$; $d = 0.91$) after the AI task. These results were seen despite PA being higher than NA for both conditions. The STAXI-2 Anger State (total score) increased significantly from pre-AI to post-AI (t (33) = −4.3, $p < 0.001$; $d = 0.74$).Table 1

3.1.2. Cardiovascular and endocrine responses

We observed a significant increase in both SBP and DBP levels after the AI task. For SBP: t (33) = −4.86, $p < 0.001$; $d = 0.83$; and for DBP: t (33) = −5.40, $p < 0.001$; $d = 0.93$. On the contrary, HR scores did not show significant differences. We observed also a significant increase in T levels (t (33) = −2.51, $p < 0.01$; $d = 0.42$) and a significant decrease in C levels (t (33) = 5.49, $p < 0.001$; $d = 0.94$).

3.1.3. Dichotic listening

There was a significant main effect of Ear (F (1, 33) = 103.2, $p < 0.001$), indicating a right ear advantage (REA) in both conditions, before and after the AI; and a significant main effect of Moment (F (1, 33) = 24.79; $p < 0.001$), indicating a higher number of correct syllables after the AI in both ears. The interaction of Ear x Moment was significant (F (1, 33) = 10.57, $p < 0.003$). The post hoc analyses revealed a significant increase in RE items from pre to post AI (t (33) = −4.36, $p < 0.001$; $d = 0.73$) whereas we observed non-

Table 1
Changes in mood, cardiovascular response, hormonal response, and functional lateralization after the anger induction task, in patients with schizophrenia.

	Baseline Mean (SD)	*Post Anger Induction* Mean (SD)	*t* test *p*
Mood scales			
PANAS Positive (PA)	25.44 (9.71)	21.12 (8.19)	< 0.001
PANAS Negative (NA)	15.03 (6.56)	21.59 (8.50)	< 0.001
STAXI-2 State Anger	18.24 (6.02)	25.91 (11.94)	< 0.001
Cardiovascular Response			
SBP	116.35 (17.35)	123.18 (20.18)	< 0.001
DBP	68.24 (10.15)	72.76 (12.35)	< 0.001
HR	85.15 (15.15)	84.24 (14.29)	n.s.
Hormonal Response			
T	204.78 (65.4)	226.34 (94.07)	< 0.01
C	5.57 (2.92)	3.90 (1.60)	< 0.001
Functional lateralization (Dichotic Listening)			
RE	33.09 (6.50)	35.94 (5.91)	< 0.001
LE	17.26 (4.85)	16.47 (4.83)	n.s.
LI (REA)	0.31 (0.20)	0.37 (0.18)	< 0.007

Note: PANAS (Positive and Negative Affect Schedule), STAXI-2 (State - Trait Anger Expression Inventory), HR (Heart Rate), SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure), T (Testosterone), C (Cortisol), RE (Right Ear), LE (Left Ear), LI (Laterality Index), REA (Right Ear Advantage).

significant differences in LE items.

3.2. Magnitude of change and comparison with controls performance (see Table 2)

Regarding mood scores, there were no statistical differences between patients and controls in subPA (t (62) = −0.89; n.s.) or subNA (t (62) = 1.11; n.s.) scales. Regarding cardiovascular response, an observation of the means seemed to indicate that the patients suffered a deeper reaction after the AI, at least for BP, and almost no change for HR. However, we performed an ANCOVA with age as a covariate and found no statistical differences between groups in subHR magnitude of change (F (1, 61) = 2.65; n.s.) and neither for subDBP (F (1, 61) < 1). We still observed a significant greater reactivity for subSBP in patients even in the corrected model (F (2, 61) = 13.18; $p < 0.001$). Regarding hormonal response, there were non-significant differences between the samples, either for subT (t (62) = 0.23; n.s.) or for subC (t (62) = −1.81; n.s.). Finally, the magnitude of change for DL scores neither differed significantly between patients and controls (t (62) < 0.5; n.s. subRE, subLE). In addition, we performed a set of planned correlations in the group of patients, to find (with Bonferroni Corrections) only two strong significant relations: an expected inverse correlation between subRE and subLE (r = - 0.77, $p < 0.001$) and, most interesting, a positive correlation between subSTAXI-2 and subNA scores (r = 0.77, $p < 0.001$). A weaker, but significant, interesting correlation was observed between subSTAXI-2 and subT too (r = 0.37, $p < 0.03$).Table 2

3.3. Relationship between clinical symptoms and anger in patients with SZ

3.3.1. Clinical predictors of trait of anger

As previously commented, the STAXI-2 Trait of Anger Scale was applied to the patients only before the AI Task, because we considered that this scale measures a stable construct that should not be influenced by the intervention. Mean (SD) and [range] scores for the Scale were 19.76 (6.8), [10–37]. Three sets of multiple Stepwise Linear Regression models were designed, with scores of the PANSS subscales, and separately for PANSS positive symptoms (1 total score + 7 subscales), PANSS negative symptoms (1 total score + 7 subscales) and PANSS psychopathology (1 total score + 16 subscales) on the dependent STAXI-2 Trait of Anger Scale scores.

Regarding PANSS positive, only the Delusions subscale was accepted by the model. This variable significantly accounted for 33% (corrected *r2*) of the Trait-Anger Scale variability [F (1, 32) = 17.2, $p < 0.001$, $\beta = 0.59$]. Regarding PANSS negative, none of the subscales was accepted by the model. Finally, for the PANSS psychopathology subscales, the best model was observed with the Poor Impulse Control subscale as the only predictor [F (1, 32) = 35.7, $p < 0.001$, $\beta = 0.72$], accounting for 51% (corrected *r2*) of the Trait-Anger variability.

Table 2
Comparison of changes in mood, cardiovascular response, hormonal response, and functional lateralization after the anger induction task, between patients with schizophrenia and control subjects. Data from controls were taken from Herrero et al. (2010).

	Patients with Schizophrenia Mean (SD)	*Control Subjects* Mean (SD)	*P*
Mood scales			
PANAS Positive (subPA)	−4.32 (6.99)	−5.77 (5.87)	n.s.
PANAS Negative (subNA)	6.56 (7.08)	8.40 (6.05)	n.s.
Cardiovascular Response			
subSBP	6.82 (8.18)	1.53 (6.15)	< 0.001
subDBP	4.53 (4.89)	2.27 (4.56)	n.s.
subHR	−0.91 (4.99)	3.20 (8.03)	n.s.
HormonalResponse			
subT	21.56 (50.14)	21.85 (48.03)	n.s.
subC	−1.66 (1.76)	−3.34 (5.07)	n.s.
Functional Lateralization Dichotic Listening			
*sub*RE	2.85 (3.81)	2.40 (3.46)	n.s.
subLE	−0.79 (3.12)	−0.60 (3.47)	n.s.
subLI (REA)	0.06 (0.12)	0.05 (0.13)	n.s.

Note: PANAS (Positive and Negative Affect Schedule), HR (Heart Rate), SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure), T (Testosterone), C (Cortisol), RE (Right Ear), LE (Left Ear), LI (Laterality Index), REA (Right Ear Advantage). The "sub" refers to the difference, by subtraction, from post to pre anger induction task, for each group.

3.3.2. Clinical predictors of the response of anger after the induction task

In order to understand the influence of clinical symptoms of SZ in the psychophysiological response to the AI task, we considered all transformed variables (subtractions) as dependent variables and performed the same analyses described above. Regarding PANSS positive scale, only the Hostility subscale was significantly related to subNA scale, with F (1, 33) = 8.5; $p < 0.006$; $\beta = 0.45$, and 18% in variability explained (corrected *r2*). When analyzing PANSS negative scale, the Stereotyped Thinking subscale significantly accounted for 19% (corrected *r2*) of the variability in subC scores (F (1, 33) = 9.04; $p < 0.005$; $\beta = 0.47$). Finally, there were quite more significant relations between the PANSS psychopathology subscales and the subtractions, most of them implicating the Anxiety subscale. This scale accounted for 16% variability (corrected *r2*) of the subSTAXI-2 scores (F (1, 33) = 7.5; $p < 0.01$; $\beta = 0.43$), and also for 15% variability (corrected *r2*) of the subNA scores (F (1, 33) = 7.1; $p < 0.01$; $\beta = 0.42$). Anxiety was also related to the physiological response of the patients: this subscale accounted for the 23% variability in Testosterone (subT) response (F (1, 33) = 10.8, $p < 0.002$; $\beta = 0.50$). When analyzing the cardiovascular response, we found a combined model of Anxiety plus Disorientation related to the subSBP score (F (2, 33) = 8.3; $p < 0.001$; $\beta = 0.49$ for Anxiety, β = - 0.30 for Disorientation), with 30% of the variability in subSBP explained by the model. In addition, the decrease in PA scores after the AI task (subPA) was predicted by a combined model of Depression and Mannierism subscales (F (2, 33) = 8.32, $p < 0.001$; $\beta = 0.35$ for Depression and $\beta = 0.41$ for Mannierism).

4. Discussion

We showed that an AI procedure, applied to men with SZ, elicited deep changes in different psychobiological parameters which resembled almost identical to those observed in a sample of healthy men who had underwent the same experimental design.

The analysis of scores assessing self-reported mood after the AI is congruent with previous research that posits anger as a negative emotion: the angrier the patients felt, the greater their negative mood. The observed pattern of self-reported mood (low PA and high NA + anger feelings) fits quite well with the definition of anger as a "negative affect that arises from the blockage of movement toward a desired goal that ought to be" (Carver and Harmon Jones, 2009). Control healthy men showed the same pattern of self-reported mood after the AI in our previous study, suggesting that the patients of SZ can be as aware as healthy people about their feelings.

Anger is not only linked to negative psychological consequences, but it also acutely increases one's short-term vulnerability to cardiovascular disease events, independent of traditional risk factors (Mostofsky et al., 2014). In addition, SZ is associated with increased cardiac mortality (Hennekens et al., 2005) possibly due to a disturbed autonomic modulation of heart rate (HR) or due to additional side effects of antipsychotic medication (Bär, 2015). A reduction in deceleration capacity of HR has been as well observed in medicated patients (Birkhofer et al., 2013). Interestingly, our sample of patients showed significant increases in BP (both Systolic and Diastolic indices) after the AI, but no changes in HR, possibly because their HR was quite high at rest (mean baseline HR 85 beats/min). A closer view of our previous study shows a healthy (and younger) sample of men with a lower baseline HR (71 beats/min). This fact could increase itself the risk for cardiovascular events in patients (Zhang et al., 2016). Moreover, the comparison with the controls showed, at first sight, a greater effect of the AI in BP for patients (higher magnitude of change) though this was in part due to the difference in mean age of the samples. Taken together, these data point to the clinical need for training in controling anger and negative feelings in SZ (for instance, see the benefits of CBT in Haddock et al., 2009) to prevent cardiovascular diseases due to the especial cardiac sensitivity of these patients.

Regarding psychoendocrine variables, we found, by controlling circadian rhythms, a significant increase in T levels and a significant decrease in C levels in SZ patients after the AI. The study of neurosteroids in SZ is important because of many reasons. It has been suggested that an aberrant signaling related to T (among others) may contribute to the development of SZ and impact sex differences observed in this disorder (Owens et al., 2018). Patients with first-episode psychosis (FPE) and patients with acutely relapsed SZ (but not chronic patients) showed significantly higher levels of free T in a very recent meta-analysis (Misiak et al., 2018). In addition, a hyperactivity of the HPA axis with higher C levels and a blunted C awakening response has been shown in FPE SZ patients (Mondelli et al., 2010). The above data have been argued by authors by suggesting the etiology of SZ in part as a response to stress which changes after the treatment with antipsychotics. It is relevant to note here that we studied medicated patients: most antipsychotics have the potential of affecting both levels of T, inhibiting the HHG axis due to hyperprolactinemia (Drobnis and Nangia, 2017) and C, reducing the commented HPA hyperactivity (Handley et al., 2016) thus being a limitation of our present data. In any case, our sample of medicated patients showed salivary T levels into the range of normal population (Keevil et al., 2017). In addition, and to sum up, the suggested connection of T with stress in SZ is interesting because, as commented in the introduction, a rise in T with a fall in C have been proposed to jointly regulate proactive aggressive behavior in what is called "a dual-hormone hypothesis" (Metha and Prasad, 2015; Montoya et al., 2012; van Honk et al., 2010). The results of our previous study with healthy men are in line with this hypothesis, and the present data extend the conclusions to medicated patients suffering from SZ. Moreover, it would be of worth to extend this experimental study to drug naive or drug free patients with SZ to explore their hormonal reaction to the AI task.

In addition, we analyzed the consequences of anger experience upon perceptual asymmetry when measured with a non-emotional laterality task (verbal DL). The results showed enhanced REA after the AI, due mainly to an increase in right ear items. The verbal input in DL is a well-known stimulus-driven bottom-up material that produces a REA (it activates the processing of the left hemisphere). As a consequence of the task, we observed that anger reinforced such asymmetry effect, by means of a top-down regulation, and increased the REA, which would indicate greater left hemisphere activity after the AI (Hugdahl, 2003). The data agree with the motivational direction model of anger affect, which has posited that the left frontal brain region is involved in the experience and expression of approach-related emotions, like anger (Harmon-Jones et al., 2006, 2007). Using the same paradigm for inducing anger and a metabolic (more direct) methodology to measure brain lateralization, Marci et al. (2007) reported increased activity in the left orbitofrontal cortex and left insula together with increased HR.

As a second important aim in this study, we were interested in the influence of the clinical symptomatology of the patients in their reaction to the AI task. Based in the literature, we hypothesized that positive symptoms, especially delusions, hallucinations, hostility and lack of insight, would be significantly related to anger scores and the intensity of the patient's reaction after the AI (Witt et al., 2013). However, while we found a significant relation between one core symptom of schizophrenia -the delusions- and the STAXI-2 score measuring *Trait of Anger*, we found none of the positive symptoms were related to the increase in anger feelings or any of the physiological measures *after* the AI. Only the hostility factor came out as a predictor for a higher increase in negative mood. Thus, one could deduce that psychosis "per se" does not necessary increase the chance for an increasing in anger when faced to a relevant trigger (though if having a high hostility profile, it could do so). Another suggested factor related to anger and violence is impulsivity, both in normal people (Carré et al., 2017) and in psychotic illness (Hoptman, 2015; Krakowski and Czobor, 2017; Witt et al., 2013). Again, we found poor impulse control significantly related to trait anger, but no evident relation of impulsivity with a higher reaction of anger to the AI. Maybe the concrete situation of "anger in the lab" could account this difference, with a scenario that may represent an important restrain to stay under control even for the most impulsive individuals.

Anyway, and over the findings discussed above, the connection of anxiety levels, a symptom of psychopathology indicating poor emotional regulation, with the response of the patient after the AI, was of more interest. Anxiety not only predicted the increasing in anger feelings and negative affect after the AI, but, remarkably, it also predicted the increasing in T levels and cardiovascular reactivity (SBP). Others have also shown an association between higher anger expression and higher anxiety levels in patients with schizophrenia (Ringer and Lysaker, 2014). Thus, the psychophysiological response of our patients to the task, as a whole, could be described as anger triggered by an unavoidable stressful situation which affected particularly to those patients with poor emotional regulation. In addition, some other findings were also interesting: stereotyped thinking predicted a greater decreasing in C after the induction. Stereotyped thinking, which is cognitive in nature, has been observed elsewhere as the most significant predictor of a poor social cognition performance, among the negative symptoms of psychosis (Piskulic and Addington, 2011). So, such relation with C levels could represent part of that stressful reaction to the task, more evident for one part of the sample of patients. An additional observed relation, the depression and mannerism scores as a significant predictor for a higher decrease of positive feelings after the AI task, adds valuable information to the view of anger as a negative experience that affects more to those patients with problems of disturbed emotional regulation. In sum, our data set fits well with the "Anger

Avoidance Model" (Gardner and Moore, 2008) proposed to understand the construct of clinical anger. In essence, this model places clinical anger as a mixed emotional disorder manifesting the heightened distress found in both anxiety and mood disorders. We point that these emotional factors would act in SZ as mediators between the psychosis *per se* (psychotic symptomatology) and the feeling of increasing anger as a reaction to a given trigger, which would enhance the probability of an act of aggression in a real situation (Reagu et al., 2013). We suggest it could be of worth to perform a deeper exploration of this possibility in the future.

Conflict of interest

None

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.044.

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